**CASE REPORT**

**Aspergillus endophthalmitis: an unusual complication of disseminated infection in renal transplant patients**

S. Schelenza,*, D.J.A. Goldsmith

*a*Department of Infection, Guy’s and St Thomas’ Hospital, Lambeth Palace Road, London SE1 7EH, UK

*b*Renal Unit, Guy’s and St Thomas’ Hospital, Lambeth Palace Road, London SE1 7EH, UK

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**KEYWORDS**

Aspergillus; Endophthalmitis; Renal transplant

Summary

Endogenous Aspergillus endophthalmitis (AE) is a rare complication of invasive aspergillosis (IA) in transplant patients. In this report, we describe two patients with polycystic kidney disease, who developed AE with cerebral involvement after renal transplantation. Both patients received intense immunosuppression with methyl prednisolone and mycophenolate mofitil (MMF) because of persistent rejection, which rendered them diabetic and vulnerable to opportunistic infections. Endophthalmitis developed within six months of transplantation and was confirmed by microscopy and culture of the vitreous fluid. Patients were treated with combinations of different anti-fungal agents including liposomal amphotericin B, 5-flucytosine, itraconazole, voriconazole and terbinafine.

In an electronic MEDLINE review, we found eight further cases of AE in renal transplant patients between 1999 and September 2002. Based on this review, we identified possible risk factors including CMV infection, diabetes mellitus and treatment for rejection with agents such as methyl prednisolone and MMF. In 70% of cases the histology, microscopy or culture of vitreous fluid confirmed the diagnosis. The outcome of AE in renal transplant patients was poor with 70–100% mortality. The review of reported cases and current practice guidelines suggests that vitrectomy and intravitreal amphotericin B is the treatment of choice. In addition, new antifungal agents with good CSF and ocular penetration such as voriconazole should be considered for the treatment of invasive cerebral/ocular aspergillosis.

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**Introduction**

*Aspergillus* sp. is a ubiquitous mould causing life threatening infections primarily in the immunocompromised host. In renal transplant patients *Aspergillus* is the commonest cause of systemic fungal disease with an incidence ranging from 0.4 to 2.4% and a high mortality of 56–100%. The lungs or sinuses are usually the primary site of infection and dissemination to other organs particularly the
central nervous system can occur.\textsuperscript{2,5} We describe two cases of endophthalmitis as a rare complication of disseminated aspergillosis in renal transplant recipients. Based on a review of previous published cases we discuss possible risk factors, laboratory diagnosis and the role of new antifungal agents in the treatment of endogenous \textit{Aspergillus} endophthalmitis (AE).

### Methods

A systematic search of the English and German literature for cases of AE was performed using the MEDLINE (National Library of MEDICINE, Bethesda, MD) and cross-referencing articles to include articles published prior 1966. The time period searched was from 1959 to September 2002. The search included the following key words: \textit{Aspergillus}, endogenous, eye and endophthalmitis.

Cases were included if \textit{Aspergillus} spp. were cultured or if hyphae (suggestive of \textit{Aspergillus} spp.) were seen on microscopy in specimens from the anterior or posterior part of the eye in renal transplant patients. Cases with any evidence of exogenous trauma or operation to the eye were excluded. All cases were scrutinized for demographic information, diagnostic methods, risk factors, evidence of dissemination to other organs and outcome.

Itraconazole levels were measured by HPLC at the Public Health Laboratory Mycology Reference laboratory, Bristol UK.

### Case report 1

A 47-year-old Caucasian man had received a cadaveric renal transplant for his underlying end stage polycystic kidney disease in September 1999. Immunosuppression was intense (Table 1) because of persistent rejection. As part of his routine immunosuppression regimen he received daily prednisolone (0.3 g/kg/day for the first month, 0.2 g/kg/day for the second month, 0.15 g/kg/day for the third month and 0.1 g/kg/day thereafter). In addition to these corticosteroids, he received methylprednisolone to treat acute kidney rejection (1 g/day for three days at day 17, 50, 70, 83 and 1.5 g at day 102 post transplantation). At about four months post-engraftment he presented with general malaise and tiredness. At the time he also suffered from steroid induced insulin dependent diabetes mellitus (IDDM) and smoked 20 cigarettes per day. An antigen blood test for cytomegalovirus (CMV) was performed and found positive. Clinically he had no signs of CMV organ disease and a fundoscopy was normal. However, after a repeated positive CMV-direct antigen test result, the patient was admitted and treated with intravenous (iv) ganciclovir for presumed CMV reactivation. Seven days into his admission he developed a productive cough, pyrexia (38.2 °C) and a left upper lobe consolidation on chest X-ray. He had a raised WBC (18.4 × 10^9/l) with a neutrophilia (17.5 × 10^9/l) but a low lymphocyte count (0.7 × 10^9/l) and a raised creatinine (295 µmol/l) and CRP (339 mg/l). A bronchioalveolar lavage grew \textit{Aspergillus fumigatus} and he was commenced on liposomal amphotericin B (3 mg/kg) for presumed invasive pulmonary aspergillosis. His mycophenolate mofetil (MMF) was stopped and FK506 and prednisolone reduced. Over time his chest X-ray showed signs of cavitation and a CT imaging demonstrated air-crescent signs of the pulmonary lesion. However, on day nine he developed peri-orbital pain and severe headache. A contrast enhanced magnet resonance image (MRI) of the brain was performed demonstrating multiple ring enhancing lesions in both cerebral hemispheres with signs of ventriculitis (Fig. 1). The differential diagnosis of cerebral toxoplasmosis, aspergillosis or neoplasm was made and the patient started antitoxoplasma treatment.

Within days, the ocular pain worsened and he developed blurred vision in his right eye. On examination his visual acuity in the right eye was 1/52, and a sub-retinal white mass and pre-retinal haemorrhage was seen on fundoscopy. The fundus of the left eye was clear. Vitrectomy of the right eye was performed and branching hyphae were seen on direct microscopy (Fig. 2). Fungal hyphae and polymorphonucleocytes were also present on a PAS and Grocott stained vitreous fluid. \textit{A. fumigatus}

### Table 1  Details of the immunosuppression used in the two cases.

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction immunosuppression</td>
<td>P, A, CyA</td>
<td>P, A, CyA</td>
</tr>
<tr>
<td>First cellular rejection (days)</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>First vascular rejection (days)</td>
<td>n/a</td>
<td>10</td>
</tr>
<tr>
<td>Total cellular rejections (n)</td>
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<td>4</td>
</tr>
<tr>
<td>Methylprednisolone (grams)</td>
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<td>9</td>
</tr>
<tr>
<td>Total cumulative steroid dose (grams)</td>
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<td>11.3</td>
</tr>
<tr>
<td>Time to tacrolimus (days)</td>
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<td>19</td>
</tr>
<tr>
<td>Time to mycophenolate mofetil (days)</td>
<td>52</td>
<td>32</td>
</tr>
<tr>
<td>Time to ATG (days)</td>
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<tr>
<td>Time to CMV (days)</td>
<td>114</td>
<td>n/a</td>
</tr>
<tr>
<td>Time to diabetes mellitus (days)</td>
<td>106</td>
<td>45</td>
</tr>
<tr>
<td>Time to aspergillosis (days)</td>
<td>120</td>
<td>112</td>
</tr>
<tr>
<td>Time to death (days)</td>
<td>227</td>
<td>143</td>
</tr>
</tbody>
</table>

P, prednisolone; A, aziathioprine; CyA, cyclosporin A.
sensitive to amphotericin B and itraconazole was subsequently isolated from culture. Endogenous AE was diagnosed and the dose of amphotericin B increased (6 mg/kg) and oral flucytosine (5-FC; 40 mg/kg) added to the treatment regimen.

A subsequent brain biopsy of the ring enhancing lesions was performed to exclude secondary pathology. PAS and Grocott stained brain biopsy showed clusters of septate hyphae branching at acute angle consistent with cerebral aspergillosis; his treatment for toxoplasma was stopped.

After 57 days of anti-fungal treatment the patient improved clinically. His headache, cough and pyrexia were less severe and he was also able to distinguish light/dark in his right eye though his visual acuity was not restored. Because of his clinical improvement, his amphotericin B and 5-FC was changed to oral itraconazole (200 mg bd). After 32 days treatment with itraconazole a MRI was repeated and showed a reduction of the brain lesions. The itraconazole pre-dose serum levels were 0.73 mg/L at the beginning and 5.5 mg/L towards the end of the treatment when he also showed some side effects (nausea, vomiting and abdominal pain) but no obvious signs of interactions with other drugs. However, three month after his admission he deteriorated neurologically, presenting with confusion and left sided weakness of both limbs. A CT of his brain confirmed progressive massive dilatation of the right ventricle possibly due to outlet obstruction. Itraconazole was stopped and he was recommenced on 5-FC and liposomal amphotericin B for two weeks followed by high dose itraconazole (400 mg bd). He deteriorated a second time presenting with increased weakness in his legs and a MRI showed increased signs of a hydrocephalus. At this point it was unclear whether his clinical signs were due to ongoing active fungal disease. He was, therefore, restarted on oral 5-FC and iv liposomal amphotericin B for 17 days and then changed again to oral voriconazole (200 mg bd). After one week of voriconazole he showed persistent radiological evidence of cerebral aspergillosis and the dose was increased to 300 mg bd. However, after a total of five and a half month of treatment with various anti fungal agents, a repeat MRI demonstrated a reduction of the brain lesions. He continued a course of six weeks voriconazole mono therapy, but deteriorated clinically for the third time presenting with a left sided weakness, vomiting, drowsiness and intermittent confusion. His antifungal therapy was changed once more to liposomal amphotericin B (6 mg/kg) and oral terbinafine (500 mg od) and a ventriculo-pleural shunt was inserted to relieve the intracranial pressure. CSF specimens which were taken were abnormal showing WBC 33 × 10^6/l, RBC 14 × 10^6/l, Protein 0.5 g/l but no fungi were seen on microscopy or isolated on culture. He initially responded well but 10 days after the shunt insertion he became febrile (39 °C), confused and was diagnosed with a methicillin resistant Staphylococcus aureus (MRSA) shunt infection (CSF: WBC 280 × 10^6/l, RBC 800, Protein 0.5 g/l). He was commenced on iv vancomycin (1 g) and rifampicin (600 mg). His antifungal drugs were continued but he died three weeks later of presumed MRSA cerebral shunt infection. The cause of death remains uncertain since a post mortem was not performed.

Case report 2

A 56-year-old Caucasian man received a cadaveric renal transplant for underlying end stage polycystic kidney disease in March 2000. Within the first month
of his transplanted kidney a biopsy showed signs of vascular and cellular rejection and he was treated with methylprednisolone (1 g/day for three days at day 10 and 15 post transplantation) and antilymphocyte globulin (ALG) in addition to his prednisolone (given at the same dose regimen as case one), azathioprine and cyclosporin A. After ongoing severe rejection he received further anti-rejection treatment with additional methylprednisolone (1 g/day for three days at day 37 post transplant) and tacrolimus. The specific details of the patients’ immunosuppression are given in Table 1. The combination of corticosteroids and tacrolimus rendered him diabetic and he became insulin dependent.

Three months post renal transplantation he presented with a five day history of mid-frontal headache, nausea and vomiting. He was febrile (38.2°C) and his blood test showed normal WBC (10 x 10^9/l) and neutrophils (8.8 x 10^9/l), low lymphocyte count (0.4 x 10^9/l) and a raised CRP (52 mg/l). On examination he had cerebellar signs with nystagmus and right sided weakness. A contrast MRI brain image showed multifocal lesions in the left cerebral and right cerebellar hemisphere (Fig. 3). The differential diagnosis of cerebral toxoplasmosis or fungal infection was made and the patient started on anti-toxoplasma (sulfadiazine and pyremethamine) and anti-fungal treatment (liposomal amphotericin B 3 mg/kg/day; oral 5-FC 500 mg od). His immunosuppressive drugs (prednisolone, MMF and tacrolimus) were discontinued.

A week after admission he complained of fuzzy vision in his eyes and retinitis was noted on fundoscopy. A vitreous biopsy showed scanty pus cells but no organisms were seen. Scanty grows of *A. fumigatus* was cultured after three days incubation. Intravitreous amphotericin B was given (5 mcg) at the time of biopsy. After careful review of his vitreous specimen, dichotomous branching hyphae and polymorphonucleocytes were seen in Giemsa stain consistent with AE (Fig. 4). The toxoplasma therapy was discontinued.

Two weeks after his admission he deteriorated and developed a fluctuating level of consciousness. His amphotericin B was increased to 5 mg/kg and iv voriconazole (6 mg/kg bd loading dose followed by 4 mg/kg bd) was added. After a total treatment period of two weeks with amphotericin and 5-FC both drugs were stopped and monotherapy with voriconazole continued. His pyrexia settled after three weeks of antifungal therapy but he deteriorated clinically. He no longer opened his eyes or responded to verbal commands or pain and was increasingly hypotensive. He was admitted to the intensive care unit where he needed ventilation. A repeated MRI showed progression of his brain lesions with no signs of a hydrocephalus. It was decided not to resuscitate him and he subsequently arrested and died five weeks after admission. No post mortem was performed.

**Discussion**

In this report we describe two patients with polycystic kidney disease who developed endogenous AE after renal transplantation. Endogenous endophthalmitis is a rare cause of *Aspergillus*
infection and is mostly seen in immunocompromised patients including those suffering from AIDS,6 leukemia,7 connective tissue disease8 and solid organ transplantation9–11 but has also occurred in iv drug users,12–13 cardiac surgery14 and chronic lung disease patients.15 The incidence of AE is not known but a recent study identified 89 cases over the last 50 years with 23% occurring in solid organ transplant patients.15 Although *Aspergillus* is the most common cause of invasive fungal infection in renal transplant patients with an incidence of 0.4–2.4%,1–3 endophthalmitis is a rare occurrence. We have undertaken an electronic MEDLINE review of German and English literature and identified eight further case reports of AE in renal transplant patients between 1959 and September 2002 in addition to our two cases (Table 1).8,16–18 The review of the ten cases suggests a number of factors that may be associated with the development of AE in renal transplant patients.

Our two patients presented within the first six months post renal transplantation with non-specific symptoms such as blurred vision and headache. This is very similar to the other eight reported cases with an average time of clinical presentation of 3.3 month post transplantation.

Both our patients received intense immunosuppression including methylprednisolone and MMF because of persistent rejection, which rendered them vulnerable to opportunistic infections, although they were not neutropenic. Four out of five reviewed cases developed kidney rejection and were treated with immunosuppressive anti-rejection therapy prior to the development of AE. Recent studies provide evidence that the use of MMF, a purine synthesis inhibitor used for immunosuppression in transplant patients, is associated with a higher incidence of infections including CMV19–21 and *Aspergillus*.21 CMV infection in itself has been suggested to predispose to aspergillosis in transplant recipients and indeed one of our patients developed CMV prior to his aspergillosis.22,23

Renal transplant patients are often routinely treated with prednisolone or methylprednisolone during an episode of acute rejection. Corticosteroids are known to inhibit macrophage and neutrophil function, which are the most important cell types in the host defence against *Aspergillus*.24–26 A previous case-control study has clearly demonstrated that corticosteroids are an important risk factor for aspergillosis in renal transplant patients.27 A recent review showed that 43% of all AE cases (36/84) had received corticosteroids.15 In addition to the direct effect of corticosteroids on the host immunity, long term treatment can lead to diabetes, which predisposes to *Aspergillus* infection.28,29 Many of these risk factors have been well described in association with invasive aspergillosis (IA) but may predispose particularly to cerebral or ocular infection. In retrospect, we feel that renal transplant patients who experience ongoing severe vascular and cellular rejection requiring intense immunosuppression one has to consider carefully whether to proceed with intense immunosuppression or to risk a failure of transplantation as the risk of fatal IA would otherwise increase drastically.

The prognosis of endogenous EA in renal transplant patients is poor as the fungus has often disseminated already to other sites and recovery of vision is unlikely due to extensive retinal necrosis and choroidal damage.8 In our review of 10 AE renal patients, seven were investigated for other organ involvement and all had dissemination to organs including the brain, heart, lung, thyroid, gastrointestinal tract, skin or lung (Table 2). The mortality was 70% with only three out of 10 patients surviving their episode. Central nervous system involvement is the most common other organ affected in AE cases and can occur in up to 64%.8 A recent autopsy study has found that by the time patients are hospitalised with IA, the brain is already the commonest site of dissemination (36%) but unfortunately ocular involvement is often not investigated and thus AE may be under diagnosed.30 Patients with known risk factors should, therefore, be carefully investigated and monitored for invasive fungal infections.

Clinically the infection often begins in the posterior part of the eye as the hyphae invade the retina and the choroids leading to choroidoretinitis. The invasion of small blood vessels can cause haemorrhages and necrosis of the retina followed by a breakthrough into the vitreous leading to blurred and impaired vision. The anterior segment of the eye is often deceptively quiet although pain, photophobia and an iridocyclitis can occur. In one study, five out of 14 patients had clinical signs of invasion into the anterior chamber (hypopyon).17

The investigation of IA includes CT imaging of the chest for suspected invasive pulmonary aspergillosis and MRI imaging of the brain if symptomatic although ring enhancing lesions are indistinguishable from other infectious causes such as bacterial brain abscess or cerebral toxoplasmosis.

Serology, such as the galactomannan antigen tests may be of use in transplant patients31 and recent studies have shown that galactomannan can be detected in cerebrospinal fluid in patients suspected of cerebral aspergillosis.32 However, the usefulness of this test in the diagnosis of AE needs to be evaluated.
A definite diagnosis of IA is based on histology and culture of specimens from sterile sites but specimens such as brain or lung tissue biopsies are not always obtainable. However, in our two cases, we were able to confirm the diagnosis of disseminated IA due to microscopy and culture of vitreous biopsy material. Although endophthalmitis is rare, early fundoscopy and vitreous biopsy may play an important role in the diagnosis of AE. Vitreous material can be obtained easily and examined by direct microscopy or histology and culture. In six out of the ten reported AE cases *A. fumigatus* has been successfully isolated by culture of the vitreous and eight cases were confirmed by histology of the material. The diagnosis of EA may even be further improved by the use of specific fungal molecular diagnostic tests.33

The standard treatment for empirical, proven or suspected IA is amphotericin B.34 However, our two cases illustrate the difficulty in treating IA with cerebral and ocular involvement. Amphotericin B and itraconazole have a poor intraocular penetration35–37 and AE has occurred in our case as well as in one other case while on systemic amphotericin B treatment.36 Current practice guidelines for the treatment of AE suggest, therefore, intravitreal amphotericin B (10 μg dose) in conjunction with vitrectomy.34 Some patients with IA presenting with pulmonary or cerebral symptoms may also not express ocular symptoms at the beginning and fundoscopy is not often part of the examination. Our patient in case one had an abnormal fundoscopy finding but at the time fungal endophthalmitis was not suspected and intravitreal amphotericin B was, therefore, not given. In such circumstances amphotericin B can be injected into the vitreous at a later point.

The question is, whether one should use a systemic anti-fungal agent with good ocular penetration at the beginning of suspected aspergillosis or even as prophylaxis in high risk patients. There are new antifungal drugs, which may prove to be useful in single or combination treatment of AE. The triazole voriconazole has fungistidal action against *A. fumigatus* and has been found in aqueous humour38 and in radiolabeled form in the retina (personal communication, Peter Troke). Another new anti-fungal agent caspofungin belonging to the group of echinocandins has also fungicidal activity against *Aspergillus* but there is no data as yet as to whether it reaches effective concentrations in the eye.39

In our first patient, we also used terbinafine in combination with amphotericin B both of which have been shown to have synergistic interaction against *Aspergillus* in vitro.40 Although our patient

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Species</th>
<th>Ocular involvement</th>
<th>Onset post tx (month)</th>
<th>Laboratory diagnosis</th>
<th>Other infected organs</th>
<th>Risk factors</th>
<th>Rejection of kidney</th>
<th>Outcome</th>
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<tr>
<td>30</td>
<td>F</td>
<td>NK</td>
<td>Bilateral</td>
<td>NK</td>
<td>Died</td>
<td>CNS, H, GIT</td>
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<td>48</td>
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<td>Yes</td>
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<tr>
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<td>L, CNS</td>
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<td>Died</td>
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</table>
did not have a PM we believe that on the basis of clinical and radiological improvement he made a good response to our treatment regimen but unfortunately developed a hydrocephalus and died of complications presumably caused by a bacterial shunt infection. The treatment included a number of different anti-fungal drugs but we cannot say for sure which one of them was the most effective.

We feel there is the need for more clinical studies on the effectiveness of new anti-fungal agents in the treatment of AE and the usefulness of combination therapy. There is also no study as to whether the new antifungals could prevent serious complications such as AE in at high-risk groups if used as a prophylaxis. Anti-fungal prophylaxis with amphotericin B or itraconazole in liver transplant patients have shown some effect in preventing fungal infections, although no beneficial effect on survival could be documented.41,42

In conclusion, renal transplant patients may be at greater risk in developing EA if they receive rejection treatment with MMF or methylprednisolone19–21 or if they suffer from CMV infection,22,23 or diabetes.28,29 Our two cases illustrate that, patients presenting with non-specific ocular symptoms and those suspected with cerebral aspergillosis should be investigated for AE. A vitreous biopsy for culture, microscopy and histology may aid early diagnosis. The small number of cases reported in the literature and the diversity in treatment regimens and outcomes makes the identification of optimal therapy difficult. Nevertheless, based on recent case reports and practice guidelines, the best treatment of AE seems to include early vitrectomy and intravitreal amphotericin B injection. In addition, new antifungal agents with good CSF and ocular penetration such as voriconazole should be considered for the treatment of invasive cerebral/ocular aspergillosis.

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